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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

RE: DOCKET 00D-1350
Comments to Draft Guidance

Dear Sir or Madame:

Reference is made to the draft guidance entitled "Combined Oral Contraceptives-Labeling for Healthcare Providers and Patients" Docket 00D-1350. Although we realize that the deadline for submission of comments was September 8, as per several conversations with Lana Pauls in August and a telephone conversation with Terri Rumble, Chief, Project Management Staff on September 15, we were granted permission to have comments considered if sent in by October 1. The R.W. Johnson Pharmaceutical Research Institute and Ortho-McNeil Pharmaceuticals, affiliates of the Johnson & Johnson family of companies, welcome the opportunity to comment on proposed labeling for combined oral contraceptives (COCs).

The new proposed labeling has been reviewed and comments provided herein. General comments on the document have been provided, followed by specific comments on the content of particular sections of labeling.

GENERAL COMMENTS

1. In general, the proposed draft guidance simplifies the language describing warnings, contraindications and precautions. While we support efforts to write useful, clear product labeling that best facilitates safe and effective use of drug products, there can be disadvantages to oversimplifying language regarding risks. Specific language has been deleted from the proposed draft guidance and conclusions inserted regarding certain risks, which have the effect of making risk/benefit judgements on behalf of the healthcare provider. As a commercial marketer, we believe it is our responsibility to objectively relate the risks of oral contraceptive use so as to fairly and adequately inform those who prescribe our product. This includes the scientific basis for such where appropriate, thus allowing the healthcare provider to make his or her own clinical decision regarding the appropriate patients to receive the product. Therefore, many of our comments to the draft guidance recommend use of more specific and explicit

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language to better inform the healthcare provider regarding the risks and benefits of combined oral contraceptives.

2. A number of estrogens and progestins are contained in combined oral contraceptives, which have somewhat different pharmacologic effects, mechanisms of action, potency and risks. While we recognize the value of class labeling, we believe that allowance should be made for inclusion in labeling of these product differences. For instance, we believe that some latitude should be given for including product-specific information in certain sections: Clinical Pharmacology, Indications and Usage, Warnings and Precautions.

3. We note that the draft labeling does not appear to allow for a clinical trials section to be included in COC labeling. We believe it is important to allow the inclusion of clinical trial information, including scope of clinical trials used to evaluate a new product and any differences observed to an active comparator or placebo. New and novel estrogens and progestins could have unique characteristics which would affect a risk/benefit assessment. Disclosure of such known information would be useful to the prescriber.

4. We are uncertain as to the rationale for the sequence in which FDA has listed warnings and precautions in the draft labeling. We recommend that FDA reorder the Warnings and Precautions sections to reflect the order of greatest to least severity and/or frequency. Our proposed order is reflected in the comments for these sections below.

5. We note that FDA did not list the references that support the changes made to the draft labeling. Although we have relied upon the published scientific literature in analyzing the proposal, complete evaluation of this document is very difficult without knowledge of the scientific bases for FDA's proposals. We recommend that FDA disclose the references to the literature it relied upon to modify labeling content.We also advocate retention of the References section so that we can have a full understanding of the agency's position regarding certain portions of its recommendations.

SPECIFIC COMMENTS

Indications and Usage Section

1. Proposed revision is directed toward the section "Indications and Usage," under the heading "Indications" (page 2). The proposed text in the draft guidance is the following:

> *Combined oral contraceptives (COCs) are indicated for the prevention of pregnancy.*

We believe that specification of use by women will avoid confusion with the possibility that a male contraceptive pill might be introduced in the future. The following revision is therefore submitted for your consideration:

> *Combined oral contraceptives (COCs) are indicated for use by women for the prevention of pregnancy.*

2. Proposed revision is directed toward Table 1 in the "Indications and Usage" section (page 3). We recommend that this table be updated when efficacy data for new methods of contraception become available.

3. Proposed revision is directed toward the section "Indications and Usage," under the heading "Efficacy" from the draft guidance. In Table 1 (page 3 and 4), the line reading:

> *Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%[9].*

should be deleted because of the lack of definition of "75%" - "75%" compared to what? Thus, is the resultant risk of pregnancy 25% (per act of intercourse) or 25% of the risk if someone had been using combination OCs?, etc.

Also from Table 1 (page 3 and 4) the footnote number 9 reading:

> *The treatment schedule is one dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the first dose. The Food and Drug Administration has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral (1 dose is 2 white pills); Alesse (1 dose is 5 pink pills), Nordette or Levlen (1 dose is 2 light orange pills), Lo/Ovral (1 dose is 4 white pills), Triphasil or Tri Levlen (1 dose is 4 yellow pills) (62 FR 8612; February 25, 1997).**

should be deleted because we believe these references to emergency contraception should only be included in the labeling of those drugs FDA has concluded to be safe and effective for this use. We believe it is inappropriate to list dosing information on other products in the "Indications and Usage" section of a combined OC.

Contraindications Section

4. Proposed revision is directed toward the section "Contraindications" (page 4). The proposed labeling presently in the draft guidance is the following:

> *Deep vein thrombosis (current or history)*
> *Pulmonary embolism (current or history)*

We propose the revision of the wording of these categories. We believe that deep vein thrombosis is not sufficiently inclusive as it excludes non-deep vein sources and thus

does not warn appropriately for potentially serious thromboembolic events. We therefore recommend the following language:

Thrombophlebitis or thromboembolic disorders
A past history of deep vein thrombophlebitis or thromboembolic disorders

5. Proposed revision is directed toward the section "Contraindications" (page 4). The proposed labeling presently in the draft guidance is the following:

Ischemic heart disease (current or history)
History of cerebrovascular accidents

Replacement of the wording of these categories is proposed. It is believed that this wording limits it to only women who have already experienced the event rather than including women at risk for these events. The following revision is therefore submitted for your consideration:

Cerebral vascular or coronary artery disease

6. Proposed revision is directed toward the section "Contraindications" (page 4). The proposed labeling presently in the draft guidance is the following:

Headaches with focal neurological symptoms

We believe it is important to specify the disease process that has been linked with the greatest risk for morbidity. We therefore recommend the following language:

Migraine with focal aura

7. Proposed revision is directed toward the section "Contraindications" (page 4). The line reading:

Major surgery with prolonged immobilization

should not appear here because it is believed that this properly belongs in the "Warnings". We also provide specific direction to the provider as to how to manage the patient. See our proposed section under "Warnings" (comment # 17).

8. Proposed revision is directed toward the section "Contraindications" (page 4). The proposed labeling presently in the draft guidance is the following:

Liver tumors (benign and malignant), active liver disease

It is proposed that this language be replaced with the following language which is specific and distinguishes neoplasms from other liver masses and enlargements:

Acute or chronic hepatocellular disease with abnormal liver function

Hepatic adenomas or carcinomas

9. Proposed revision is directed toward the section "Contraindications" (page 5). We propose that the line reading:

Heavy smoking (>15 cigarettes per day) and over age 35

should not appear here. Similar information is contained in the boxed warning as proposed by FDA. We believe that the boxed warning in current labeling is reasonable and appropriate.

10. Proposed revision is directed toward the section "Contraindications" (page 5).

We recommend retaining the following contraindication from the 1994 Guidance Document because we are aware of no convincing evidence of safety for women with cancer of endometrium:

Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia

11. Proposed revision is directed toward the section "Contraindications" (page 5).

We recommend adding the following contraindication because a history of cholestatic jaundice in pregnancy or with prior OC use has been associated with an increased incidence of cholestatic jaundice with subsequent pill use:

Cholestatic jaundice of pregnancy or jaundice with prior pill use

12. Proposed revision is directed toward the section "Contraindications" (page 5).

We recommend adding the following contraindication because it could indicate *in utero* pregnancy, ectopic pregnancy, or vaginal or uterine cancer. OC use could mask the symptoms of these conditions and potentially delay their diagnosis:

Undiagnosed abnormal genital bleeding

13. In summation, we propose the following list of Contraindications in the following order:

CONTRAINDICATIONS

Oral contraceptives should not be used in women who currently have the following conditions:

- *Thrombophlebitis or thromboembolic disorders*
- *A past history of deep vein thrombophlebitis or thromboembolic disorders*
- *Cerebral vascular or coronary artery disease*

- *Migraine with focal aura*
- *Known or suspected carcinoma of the breast*
- *Valvular heart disease with complications*
- *Severe hypertension*
- *Diabetes with vascular involvement*
- *Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia*
- *Undiagnosed abnormal genital bleeding*
- *Cholestatic jaundice of pregnancy or jaundice with prior pill use*
- *Acute or chronic hepatocellular disease with abnormal liver function*
- *Hepatic adenomas or carcinomas*
- *Known or suspected pregnancy*
- *Hypersensitivity to any component of this product*

Warnings

14. Proposed revision is directed toward the section "Warnings" above the heading reading. "1. Cardiovascular disease" (page 5). We recommend adding the following which identifies the underlying risk factors that contribute to thrombosis as well as the potentially serious morbidities that have been reported in women using COCs:

> *The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity and diabetes.*

We also believe that sponsors should have the right to insert product specific data in this section.

15. Proposed revision is directed toward the section "Warnings" under the heading reading. "1. Cardiovascular disease" (page 5). The proposed labeling presently in the draft guidance is the following:

> *COC use is associated with an increase in the incidence of cardiovascular disease, primarily because of an increased risk of thrombosis, rather than through an atherogenic mechanism. The degree of risk appears to be related primarily to the estrogen dosage. This increased risk is limited to the period of COC use and disappears on cessation of use.*

We would appreciate FDA sharing any supporting references from the medical literature for the last two sentences in this section. In addition, we would like supportive data that discusses the lack of contribution of an atherogenic mechanism to the thrombotic process in order to assess this reduction in risk from the 1994 Guidance Document. The following revision is therefore proposed:

COC use is associated with an increase in the incidence of cardiovascular disease. The degree of risk appears to be related to the steroid hormone dosage, especially in products containing estrogen dosages greater than 35 mcg (1). Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one that contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient.

16. Proposed revision is directed toward the section "Warnings" (page 5). The proposed title of this section presently in the draft guidance is the following:

a. Deep vein thrombosis, pulmonary embolism

"Deep vein thrombosis" is insufficiently inclusive, as other types of thrombosis have been reported. The following revised title is therefore submitted for your consideration:

a. Thromboembolism including deep vein thrombosis, pulmonary embolism

17. Proposed revision is directed toward the section "Warnings" under the heading reading. "a. Deep vein thrombosis, pulmonary embolism" (page 5). The proposed text is the following:

Use of COCs is associated with a risk of venous thromboembolism which is 3 to 6 times higher than that among nonusers. Smoking does not appear to contribute to the risk of venous thromboembolic events.

This, as written, draws summary conclusions whereas the wording we suggest provides more comprehensive information:

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease (2-8). Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization (9). The risk of thromboembolic disease associated with oral contraceptives is not related to length of use and disappears after pill use is stopped (2).

A two- to four-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives (10). The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions (11). If

feasible, oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization.

Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four weeks after delivery in women who elect not to breast feed.

After an induced or spontaneous abortion that occurs at or after 20 weeks gestation, hormonal contraceptives may be started either on Day 21 post-abortion or on the first day of the first spontaneous menstruation, whichever comes first (12).

18. Proposed revision is directed toward the section "Warnings" under the subheading, "a. Deep vein thrombosis, pulmonary embolism" (page 5). The text proposed in the FDA draft guidance is the following:

The presence of factor V Leiden mutation and other hereditary coagulation disorders increases the risk of thromboembolic disease.

Narrowing the language assures that women with nonthrombogenic hereditary coagulation disorders remain eligible for hormonal contraception. The following language is submitted:

The presence of certain hereditary disorders such as factor V Leiden mutation increases the risk of thromboembolic disease in COC users.

19. Proposed revision is directed toward the subheading "For products containing desogestrel:" (page 5). Our understanding is that only the paragraph immediately following this subheading relates to products containing desogestrel. However, the placement of this heading is confusing and suggests that all warnings beneath this subheading apply to products containing desogestrel. We recommend that FDA resolve this confusion by moving this paragraph and subheading to the bottom of this section.

20. Proposed revision is directed toward the section "Warnings" under the subheading reading "For products containing desogestrel:" (page 5). We believe the lines reading:

COC use is <u>contraindicated</u> for women who have active deep venous thrombosis or pulmonary embolism and for those who have have a history of these conditions in association with estrogen use.

Women who are immobilized for prolonged periods because of major surgery <u>should not use</u> COCs. For women undergoing surgery without prolonged immobilization, the advantages of COC use generally outweigh the risk.

should be replaced because they are addressed elsewhere. See our proposed section a under "Warnings" (comment # 17).

Under the same section, we believe the lines reading:

> *COC use should preferably not begin until 2-3 weeks postpartum, because of the risk of thrombosis.*

should be replaced because it is covered elsewhere. See our proposed section a under "Warnings" (comment # 17).

21. Proposed revision is directed toward the section "Warnings" (page 6). The section reading:

> *b. cerebrovascular disease*
>
> *In women who do not smoke and do not have hypertension, the risk of ischemic stroke in users of COCs is increased by about 1.5 times compared with nonusers. The likelihood of hemorrhagic stroke is not increased among users of low dose combined COCs who are under 35 years old and do not smoke or have hypertension. Women who have a history of stroke should not use COCs.*
>
> *The likelihood of myocardial infarction (MI) is not increased among young women who use COCs and do not smoke or have hypertension or diabetes. Heavy smokers (>15 cigarettes/day) older than 35 years should not take COCs. Women who currently have ischemic heart disease, or who have a history of this disease, should not use COCs due to an increased risk of MI and stroke.*

should be replaced because it inadequately addresses smokers and women with hypertension. Risk quantification requires current citations. See our proposed section c under "Warnings" (comment #24).

22. Proposed revision is directed toward the section "Warnings," section "1. Cardiovascular disease" (page 6). We recommend adding the following as section b. in order to offer a more complete list of risk factors for this outcome and to provide a more precise quantification of the interactions between the various risk factors:

> *b. Myocardial Infarction*
>
> *An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart*

attack for current oral contraceptive users has been estimated to be two to six (10, 11; 13-18). The risk is very low under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases (19). Mortality rates associated with circulatory disease have been shown to increase substantially in smokers, especially in those 35 years of age and older among women who use oral contraceptives.

23. Proposed revision is directed toward the section "Warnings" above the section "1. Cardiovascular disease" (page 6). The section

c. Valvular heart disease

COC use is contraindicated for women whose valvular heart disease is complicated by such factors as pulmonary hypertension, atrial fibrillation, or history of subacute bacterial endocarditis. COC use may be acceptable for women with uncomplicated valvular heart disease.

should not appear here because this is covered under contraindications.

24. Proposed revision is directed toward the section "Warnings," section "1. Cardiovascular disease" (page 5). We recommend adding the following as section c because the medical literature describes an increase in the risk of hemorrhagic stroke among women using COCs:

c. Cerebrovascular diseases

Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, and smoking interacted to increase the risk of stroke (20-22).

25. Proposed revision is directed toward the section "Warnings," section "1. Cardiovascular disease" (page 5). We recommend adding the following as section d because we believe that this provides fair balance to the efficacy of OCs and information regarding the persistence of risks:

d. Persistence of risk of vascular disease

There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40-49 years who had

used oral contraceptives for five or more years, but this increased risk was not demonstrated in other age groups (17). In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small (23). However, both studies were performed with oral contraceptive formulations containing 50 micrograms or higher of estrogen.

26. Proposed revision is directed toward the section "Warnings" (page 5). We recommend adding the following as section 2 in order to provide information regarding the risk of contraceptive-related mortality:

2. Estimates of Mortality from Contraceptive Use

One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (Table IV). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke, and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth. The observation of an increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970's (24). Current clinical recommendation involves the use of lower estrogen dose formulations (containing 35 mcg or less of ethinyl estradiol) and a careful consideration of risk factors (25). In 1989, the Fertility and Maternal Health Drugs Advisory Committee concluded that although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception. The Committee recommended that the benefits of low-dose oral contraceptive use by healthy non-smoking women over 40 may outweigh the possible risks.

Of course, older women, as all women, who take oral contraceptives, should take an oral contraceptive which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and individual patient needs.

27. Proposed revision is directed toward the section "Warnings" to be inserted at the end of our proposed section "2. Estimates of Morality from Contraceptive Use." We note that FDA has omitted Table IV: "Annual Number of birth-related or method-related deaths associated with control of fertility per 100,000 non-sterile women, by fertility control method according to age." We disagree with the omission of this table because we believe there is value in including this information. Although we

acknowledge that the specific data may be somewhat dated, we believe this table should be retained and updated when possible. Furthermore, this table provides useful information which, when combined with Table 1 describing efficacy rates of various contraceptive methods, provides comprehensive and balanced information on the risks and benefits of various contraceptive methods.

TABLE IV: ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NON-STERILE WOMEN, BY FERTILITY CONTROL METHOD ACCORDING TO AGE

Method of control and outcome	*15-19*	*20-24*	*25-29*	*30-34*	*35-39*	*40-44*
*No fertility control methods**	*7.0*	*7.4*	*9.1*	*14.8*	*25.7*	*28.2*
*Oral contraceptives non-smoker***	*0.3*	*0.5*	*0.9*	*1.9*	*13.8*	*31.6*
*Oral contraceptives, smoker***	*2.2*	*3.4*	*6.6*	*13.5*	*51.1*	*117.2*
*IUD***	*0.8*	*0.8*	*1.0*	*1.0*	*1.4*	*1.4*
*Condom**	*1.1*	*1.6*	*0.7*	*0.2*	*0.3*	*0.4*
*Diaphragm/ spermicide**	*1.9*	*1.2*	*1.2*	*1.3*	*2.2*	*2.8*
*Periodic abstinence**	*2.5*	*1.6*	*1.6*	*1.7*	*2.9*	*3.6*

** Deaths are birth-related*
***Deaths are method-related*
Adapted from H.W. Ory, ref. #24.

28. Proposed revision is directed toward the section "Warnings" (page 5). The section:

> *2. Elevated blood pressure*
>
> *For women with an elevation in blood pressure (160+/100+ mm/Hg), COC use would present an unacceptable health risk, and COCs should not be used. Similarly, hypertensive women with vascular disease should not use COCs.*

should not appear here because it already appears in the contraindication section.

29. Proposed revision is directed toward the section "Warnings" (page 5)". We recommend adding the following as section 3 because a normotensive woman may develop elevated blood pressure following the initiation of product use.

> *3. Hypertension*
>
> *An increase in blood pressure has been reported in some women taking oral contraceptives (26) and this increase is more likely in older oral contraceptive users (27) and with extended duration of use (28). Data from the Royal College of General Practitioners (29) and subsequent randomized trials have shown that the incidence of hypertension increases with increasing progestational activity.*
>
> *If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the*

occurrence of hypertension between former and never users (26-27, 30-31). Women with a history of hypertension or hypertension-related diseases or renal disease (30) should be encouraged to use another method of contraception.

30. Proposed revision is directed toward the section "Warnings." The section:

3. Carbohydrate Metabolism

For women with diabetes (both insulin-dependent ad non-insulin dependent), who do not have vascular involvement, the advantages of COC use generally outweigh the risks, particularly in light of the risks associated with pregnancy in these women. The major concerns of COC use by this population are vascular disease and an added risk of thrombosis, although COC use by diabetic women appears to have only minimal effects on lipid metabolism and hemostasis. For diabetic women with nephropathy, retinopathy, neuropathy, or other vascular involvement, the risk-benefit ratio depends on the severity of the condition.

should be replaced because it is making a risk/benefit assessment that should be left to the physician. Furthermore, this assessment dilutes the warning thereby minimizing its importance and is in disagreement with the proposed contraindication. See our proposed section 9 under "Warnings" (comment # 42).

31. Proposed revision is directed toward the section "Warnings" (page 5): We recommend adding the following as section 4 because our title reflects the substance of the warning and more accurately describes the risk, particularly to the younger user who is most likely to have the longest exposure to the product:

4.Carcinoma of the Breasts and Cervix

Numerous epidemiological studies have been performed on the incidence of breast and cervical cancer in women using oral contraceptives. While there are conflicting reports, most studies suggest that use of oral contraceptives is not associated with an overall increase in the risk of developing breast cancer. Some studies have reported an increased relative risk of developing breast cancer among COC users, particularly at a younger age. This increased relative risk has been reported to be related to duration of use (32-51).

A meta-analysis of 54 studies found a small increase in the frequency of having breast cancer diagnosed for women who were currently using combined oral contraceptives or had used them within the past ten years. This increase in the frequency of breast cancer diagnosis, within ten years of stopping use, was generally accounted for by cancers localized to the breast. There was no increase in the frequency of having breast cancer diagnosed ten or more years after cessation of use (52). Breast cancers diagnosed in current

or previous OC users tend to be less invasive than in nonusers. Women who have or have had breast cancer should not use COCs because breast cancer is a hormone-sensitive tumor.

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women (53-56). However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

32. Proposed revision is directed toward the section "Warnings," The section:

4. Lipid Metabolism

Because some hyperlipidemias are risk factors for vascular disease, the appropriateness of COC use is dependent on the type and severity of known hyperlipidemias.

should be replaced because it is addressed under risk factors for thromboembolism and it does not describe the lipid abnormalities women can develop subsequent to product use. See our proposed section 9 under "Warnings" (comment #42).

33. Proposed revision is directed toward the section "Warnings" (page 5): We recommend adding the following as section 5 because it provides more specific data on the risks of developing these morbidities:

5. Liver Disease

Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years of use especially with oral contraceptives of higher dose (57). Rupture of benign, hepatic adenomas may cause death through intra-abdominal hemorrhage (58, 59).

Studies have shown an increased risk of developing hepatocellular carcinoma (60-63) in oral contraceptive users. However, these cancers are rare in the U.S.

34. Proposed revision is directed toward the section "Warnings," The section:

5. Headaches

For women with severe, recurrent headaches, including migraine headaches, the appropriateness of using COCs depends on the presence or absence of

focal neurologic symptoms. These symptoms may reflect an increased risk of stroke and COC use is contraindicated in patients in whom they are present. The onset or exacerbation of migraines or the development of severe recurrent or persistent headache with focal neurological symptoms requires discontinuation of COC use and evaluation of the cause of the headaches

should be replaced because it is addressed in contraindications and our proposed "Warnings" section. See our proposed section 10 under "Warnings" (comment #43).

35. Proposed revision is directed toward the section "Warnings" (page 5): We recommend adding the following as section 6 because of the severity of the risk, and because reports of these lesions have been received. Furthermore, this information is not covered in sections regarding deep vein thrombosis and pulmonary embolism:

6. Ocular Lesions

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

36. Proposed revision is directed toward the section "Warnings" (page 5): We recommend adding the following as section 7:

7. Oral Contraceptive Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy (64, 65). The majority of recent studies also do not indicate a teratogenic effect, particularly insofar as cardiac anomalies and limb reduction defects are concerned (64, 66-68), when taken inadvertently during early pregnancy.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion

It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued until pregnancy is ruled out.

37. Proposed revision is directed toward the section "Warnings," The section:

6. Unexplained Vaginal Bleeding

Women who have unexplained vaginal bleeding suggestive of an underlying pathological condition or pregnancy should be evaluated prior to initiation of COC use to avoid confusion of the potentially pathologic bleeding with a possible COC side effect.

Mild bleeding irregularities are common among women taking COCs, particularly during the early months of use. However, if the bleeding pattern of a COC user is suggestive of pathology or pregnancy, diagnostic measures should be taken to rule out these other causes; meanwhile, the benefits of continued COC use generally outweigh the risks.

should be replaced because discussion of medical evaluation involving proper patient selection does not belong in warnings. Also, a risk/benefit assessment is made that minimizes the importance of the warning. In addition, it does not specify the differentiation of benign from pathological bleeding. See our proposed section 11 under "Warnings" (comment #.45).

38. Proposed revision is directed toward the section "Warnings," The section:

7. Breast Cancer

Although the risk of breast cancer may be slightly increased among current and recent users of COCs, this excess risk decreases over time after COC discontinuation and by 10 years after cessation the increased risk disappears. The risk does not increase with duration of use, and no relationships have been found with dose or type of steroid. The patterns of risk are also similar regardless of a woman's reproductive history or her family breast cancer history. The subgroup for whom risk has been found to be significantly elevated is women who first used COCs before age 20, but because breast cancer is so rare at these young ages, the number of cases attributable to this early COC use is extremely small.

Breast cancers diagnosed in current or previous OC users tend to be less invasive than in nonusers.

Women who currently have or have had breast cancer should not use COCs because breast cancer is a hormone-sensitive tumor.

should be replaced because it does not accurately refect the reported medical literature regarding the risk of breast cancer. See our proposed section 4 under "Warnings" (comment #31).

39. Proposed revision is directed toward the section "Warnings," The section:

8. Cervical Cancer

Some reports indicate a statistical association between COC use and cervical cancer, but several important methodological problems are inherent in studying this relationship, and the association remains unclear.

should be replaced with language which more accurately reflects the reported medical literature. See our proposed section 4 under "Warnings" (comment #31).

40. Proposed revision is directed toward the section "Warnings," The section:

9. Gallbladder disease

COCs may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women.

Women with a history of COC-related cholestasis are more likely to have the condition recur with subsequent COC use.

should be replaced because as written, this implies that only women with underlying gallbladder disease are at risk. See our proposed section 8 under "Warnings" (comment #41).

41. Proposed revision is directed toward the section "Warnings" (page 5): We recommend adding the following as section 8 because we are unaware of any recent medical literature that would suggest that this statement should change. COCs may contribute to the development of this disease in users:

8. Gallbladder Disease

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens (69, 70). More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal (71-73). The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens

In women with a prior history of gallbladder disease, COC's should be used with caution.

42. Proposed revision is directed toward the section "Warnings" (page 5): We recommend adding the following as section 9:

9. Carbohydrate and Lipid Metabolic Effects

Oral contraceptives have been shown to cause a decrease in glucose tolerance in a significant percentage of users (74). This effect has been shown to be directly related to estrogen dose (75). Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational

agents (74,76). However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose (77). Because of these demonstrated effects, prediabetic and diabetic women in particular should be carefully monitored while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see WARNINGS 1a and 1d), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

43. Proposed revision is directed toward the section "Warnings" (page 5): We recommend adding the following as section 10 because it provides specific information to the provider as to when discontinuation is necessary:

10. Headache

The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause.

44. Proposed revision is directed toward the section "Warnings," The section:

10. Liver disease

Because steroid hormones are metabolized by the liver, women taking COCs may experience adverse hepatobiliary effects. Although case-control studies have indicated that the risk of both benign and malignant liver tumors may be slightly increased by COC use, the incidence of these tumors potentially attributable to COCs in the United States is minimal because the disease is very rare.

Women who currently have active liver disease should not use COCs.

should be replaced because it minimizes the warning and is not specific and it contains a contraindication which is already covered by our proposed list of contraindications. See our proposed section 5 under "Warnings" (comment #33).

45. Proposed revision is directed toward the section "Warnings" (page 5): We recommend adding the following as section 11 because it provides more direct information to the provider for the evaluation of this adverse event.

11. Bleeding irregularities

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy as appropriate, as in the case of

any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was preexistent.

46. Proposed revision is directed toward the section "Warnings" (page 5): We recommend adding the following as section 12 because ectopic pregnancies have been reported as occurring:

12. Ectopic Pregnancy

Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

Precautions section

47. Proposed revision is directed toward the section "Precautions" (page 8). We recommend re-ordering and re-classification as follows: 1. Physical Examination and Follow-Up 2. Lipid Disorders 3. Liver Function 4. Fluid Retention 5. Emotional Disorders 6. Contact Lenses 7. Drug Interactions 8. Interactions with Laboratory Tests 9. Carcinogenesis 10. Pregnancy 11. Nursing Mothers 12. Pediatric Use 13. Sexually Transmitted Diseases. Unless otherwise indicated below, we support the wording included in the draft guidance for the section referred to above.

48. Proposed revision is directed toward the section "Precautions" (page 8): We recommend adding the following as section 1 to provide more complete information to the physician. FDA's language suggests that blood pressure is the only important assessment. However, we believe that other parameters should be assessed and monitored in addition to blood pressure:

1. PHYSICAL EXAMINATION AND FOLLOW UP

It is good medical practice for all women to have annual history and physical examinations, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

We recommend the replacement of the draft guidance section below with the above addition:

2. Physical examination and follow-up

Before initiating COC use, blood pressure should be measured and details of the woman's personal and family medical history should be obtained. Blood pressure should be measured periodically during COC use and additional clinical evaluation should be based on these initial and follow-up findings.

49. Proposed revision is directed toward the section "Precautions." We recommend adding the following as section 2 because we believe it is important to caution physicians regarding the management of hyperlipidemias:

2.LIPID DISORDERS

Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and depress HDL levels, and may render the control of hyperlipidemias more difficult.

50. Proposed revision is directed toward the section "Precautions." We recommend adding the following as section 3:

3. LIVER FUNCTION

If jaundice develops in any woman receiving such drugs, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

51. Proposed revision is directed toward the section "Precautions." We recommend adding the following as section 4 because this is a frequently occurring effect of OCs:

4. FLUID RETENTION

Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

52. Proposed revision is directed toward the section "Precautions." We recommend adding the following as section 5 because mood changes have been reported:

5. EMOTIONAL DISORDERS

Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

53. Proposed revision is directed toward the section "Precautions." We recommend adding the following as section 6 because these effects have been reported:

6. CONTACT LENSES

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

54. Proposed revision is directed toward the section "Precautions." We recommend adding the following as section 7 since different estrogens and progestins have different metabolic pathways, and therefore different drug interaction profiles. We believe the use of uniform language in class labeling to describe drug interactions is not the optimal way to address this issue. We recommend that sponsors be allowed the opportunity to include drug interaction information that is specific to the particular compound.

In addition, we disagree with the inclusion of an interaction with ascorbic acid and acetaminophen. We believe the data on these interactions are equivocal, and, in the absence of references used by FDA to support these statements, we cannot fully evaluate this information:

7. DRUG INTERACTIONS

Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampin. A similar association, though less marked, has been suggested with barbiturates, phenylbutazone, phenytoin sodium, carbamazepine, griseofulvin, topiramate, and possibly with ampicillin and tetracyclines (78). A possible interaction has been suggested with hormonal contraceptives and the herbal supplement St. John's Wort based on some reports of oral contraceptive users experiencing breakthrough bleeding shortly after starting St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort. Some protease inhibitors and some anti-retroviral agents have been found to either increase (ex. Indinavir) or decrease (ex. Ritonavir) circulating levels of combination hormonal contraceptives (79). Healthcare prescribers are advised to consult the package inserts of medication administered concomitantly with oral contraceptives.

We therefore recommend the replacement of FDA's proposed Drug interactions section in the draft guidance below with the above addition:

3. Drug Interactions

The efficacy of COCs is reduced by hepatic enzyme-inducing drugs such as the antituberculosis drug rifampin and the anticonvulsants phenytoin, carbamazepine, and barbiturates. The efficacy of COCs when used with griseofulvin may also be reduced.

The following section contains information on drug interactions with ethinyl estradiol-containing products that have been reported in the public literature. It is unknown whether such interactions occur with drug products containing other types of estrogens.

a. *The metabolism of ethinyl estradiol is increased by rifampin and anticonvulsants such as phenobarbitol, phenytoin, and carbamazepine. Coadministration of troglitazone and certain ethinyl estradiol-containing drug products (e.g., oral contraceptives containing ethinyl estradiol) reduce the plasma concentrations of ethinyl estradiol by 30 percent.*

Ascorbic acid and acetaminophen may increase AUC and/or plasma concentrations of ethinyl estradiol. Coadministration of atorvastatin and certain ethinyl estradiol-containing drug products (e.g., oral contraceptives containing ethinyl estradiol) increase AUC values for ethinyl estradiol by 20 percent.

Clinical pharmacokinetic studies have not demonstrated any consistent effect of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.

b. *Drug products containing ethinyl estradiol may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporin, prednisolone, and theophylline have been reported with concomitant administration of certain drugs containing ethinyl estradiol (e.g., oral contraceptives containing ethinyl estradiol). In addition, drugs containing ethinyl estradiol may induce the conjugation of other compounds.*

55. Proposed revision is directed toward the section "Precautions." We recommend the following as section 8 because it provides more specific information:

8. INTERACTIONS WITH LABORATORY TESTS

Certain endocrine and liver function tests and blood components may be affected by oral contraceptives:

a. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

b. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.

c. Other binding proteins may be elevated in serum.

d. Sex hormone binding globulins are increased and result in elevated levels of total circulating sex steroids; however, free or biologically active levels either decrease or remain unchanged.

e. High-density lipoprotein (HDL-C) and total cholesterol (Total-C) may be increased, low-density lipoprotein (LDL-C) may be increased or decreased, while LDL-C/HDL-C ratio may be decreased and triglycerides may be unchanged. These effects are related to the doses of estrogen and progestin, and to progestin type.

f. Glucose tolerance may be decreased.

g. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives

We therefore recommend the replacement of the draft guidance section below with the above addition:

4. Interactions that affect laboratory tests

The following tests may be affected by COC use, with the direction and magnitude of the effect dependent in part on the type and dose of the steroids:

b. Glucose tolerance may be impaired and insulin levels increased (see CARBOHYDRATE METABOLISM).

c. Triglycerides may be increased, and levels of various other lipids and lipoproteins may be affected (see LIPID METABOLISM).

d. Various parameters of coagulation and fibrinolytic activity may be affected.

e. Thyroid-binding globulin (TBG) and protein-bound iodine (PBI) may be increased; T3 resin uptake may be decreased. Other binding globulins (corticosteroid binding globulin/CBG, ceruloplasmin, cortisol) may also be elevated in serum

56. Proposed revision is directed toward the section "Precautions", under the category : "Pregnancy". We recommend adding that COCs are considered Pregnancy Category X, consistent with 21 CFR 201.57 (f)(6)(i)(e).

57. Proposed revision is directed toward the section "Precautions." We recommend replacement of the section:

8. Fertility following discontinuation

Conception may be delayed an average of 1-2 months among women stopping COCs compared to women stopping nonhormonal contraceptive methods.

with our proposed section 11 of "Warnings" (comment #45).

Adverse Experiences

58. Proposed revision is directed toward the section "Adverse Experiences." We believe the current approach (as reflected in the Ortho-TriCyclen approved labeling) is consistent with the current regulations and guidance, and also more consistent with FDA's recent *Draft Guidance for Industry; Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics*, than FDA's current proposal. Adverse experiences should be covered separately from Warnings and Precautions.

ADVERSE EXPERIENCES

The most serious adverse reactions associated with the use of COCs are discussed above in the WARNINGS section. Others are presented in the PRECAUTIONS section.

Other side effects commonly reported by COC users are:

Nausea
Breast tenderness
Headaches
Less frequently, the following adverse reactions may occur:
Vomiting and other gastrointestinal symptoms (e.g., bloating)
Mood changes and depression
Decreased libido
Acne
Dizziness
Weight gain (or loss)
Melasma
Increased cervical ectopia
Vaginal candidiasis
Fluid retention
Ocular effects, including decreased tolerability to contact lenses

It is not always clear whether these side effects are causally associated with COCs and, if so, whether the estrogen and/or the progestin is responsible. These side effects tend to be most common in the first 1-3 pill cycles, with the prevalence declining thereafter.

Some COC users have breakthrough bleeding or spotting, although this side effect generally improves over time. Breakthrough bleeding is somewhat more

likely to occur following a missed pill. More rarely, prolonged bleeding or amenorrhea can occur. However, most women experience beneficial changes in menstrual cycle patterns (see NONCONTRACEPTIVE HEALTH BENEFITS).

In place of FDA's proposed language, we recommend the following:

Adverse Reactions

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS Section).

- *Thrombophlebitis and venous thrombosis with or without embolism*
- *Arterial thromboembolism*
- *Pulmonary embolism*
- *Myocardial infarction*
- *Cerebral hemorrhage*
- *Cerebral thrombosis*
- *Hypertension*
- *Gallbladder disease*
- *Hepatic adenomas or benign liver tumors*

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related:

- *Nausea*
- *Vomiting*
- *Gastrointestinal symptoms (such as abdominal cramps and bloating)*
- *Breakthrough bleeding*
- *Spotting*
- *Change in menstrual flow*
- *Amenorrhea*
- *Temporary infertility after discontinuation of treatment*
- *Edema*
- *Melasma which may persist*
- *Breast changes: tenderness, enlargement, secretion*
- *Change in weight (increase or decrease)*
- *Change in cervical erosion and secretion*
- *Diminution in lactation when given immediately postpartum*
- *Cholestatic jaundice*
- *Migraine*
- *Rash (allergic)*
- *Mental depression*
- *Reduced tolerance to carbohydrates*
- *Vaginal candidiasis*

- *Change in corneal curvature (steepening)*
- *Intolerance to contact lenses*

The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted:

- *Pre-menstrual syndrome*
- *Cataracts*
- *Changes in appetite*
- *Cystitis-like syndrome*
- *Headache*
- *Nervousness*
- *Dizziness*
- *Hirsutism*
- *Loss of scalp hair*
- *Erythema multiforme*
- *Erythema nodosum*
- *Hemorrhagic eruption*
- *Vaginitis*
- *Porphyria*
- *Impaired renal function*
- *Hemolytic uremic syndrome*
- *Acne*
- *Changes in libido*
- *Colitis*
- *Budd-Chiari Syndrome*

Noncontraceptive Health Benefits

59. Proposed revision is directed toward the Noncontraceptive Health Benefits section of the draft guidance proposal. We recommend the replacement of the FDA paragraph:

> *During the time that women are taking COCs, many experience the following improvements in menstrual parameters:*

with our proposed wording below because we believe that the medical literature reports are largely based on higher dose products:

> *The following non-contraceptive health benefits related to the use of combination oral contraceptives are supported by epidemiological studies which largely utilized oral contraceptive formulations containing estrogen doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg mestranol (80-85).*

Patient Package Insert

60. Proposed revision is directed toward the Patient Package Insert. Regarding the patient labeling in general, we believe that the patient package insert should reflect the final professional labeling. We will reserve further review of the patient package insert until the content of the professional labeling is known.

There is an apparent inconsistency regarding whether or not there is a clinically significant drug interaction between COCs and antibiotics. The proposed professional labeling patient package insert states, "*Clinical pharmacokinetic studies have not demonstrated any consistent effect of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.*" However, the patient package insert states, "*Antibiotics are rarely a problem, but it is a good idea to use a backup method of birth control just in case.*" The recommendation in the patient package insert implies that antibiotics do impair the efficacy of oral contraceptives, which appears to be inconsistent with the professional label. We recommend that FDA take a clear and consistent position on this issue in both documents.

We appreciate the opportunity to comment on this draft guidance, and thank FDA in advance for its thoughtful consideration of our revisions.

Sincerely,

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